

REMARKS

I. Claim Status

Claims 3-8 are currently pending and stand rejected. No claims are amended herein.

II. Obviousness Rejection

The Office rejected claims 3-8 under 35 U.S.C. § 103(a) as unpatentable over Follath et al. "Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial," *The Lancet* (2002) 360:196-202 ("Follath") in view of Perrone et al. "Serum Creatinine as an Index of Renal Function: New Insights into Old Concepts," *Clinical Chemistry* (1992) 38(10):1933-1953 ("Perrone") and Pagel, P. S., et al. "Pharmacology of Levosimendan: A New Myofilament Calcium Sensitizer," *Cardiovascular Drug Reviews* (1996) 14(3):286-316 ("Pagel"). Office Action at page 3.

According to the Office, Follath teaches "a method of treating heart failure in a human comprising levosimendan," and "that the administration of levosimendan decreases serum creatinine levels, possibly due to increased organ (e.g., kidney) perfusion." Office Action at page 3. The Office acknowledges that Follath fails to teach methods for treating "severe renal failure or reduc[ing] mortality in a mammal suffering from severe renal failure or the periodic or daily administration of levosimendan orally," and relies on Perrone and Pagel to remedy these deficiencies. *Id.* at pages 3-4.

The Office asserts that Perrone teaches that "a decrease in serum creatinine indicates increased renal function," and that Pagel teaches "the daily administration of levosimendan, orally, for the treatment of heart failure." *Id.* at page 3. The Office concludes that it would have been obvious "to orally administer levosimendan to a

mammal with severe renal failure in order to treat said renal failure . . . since administration of the drug was known to result in increased renal function . . . [and] daily oral administration was taught to be an appropriate schedule/route of administration . . .” *Id.* at page 4. Applicants respectfully disagree and traverse this rejection.

The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 415-419, 82 U.S.P.Q.2d 1385, 1395-97 (2007) identified a number of rationales to support a conclusion of obviousness which are consistent with the proper “functional approach” to the determination of obviousness as laid down in *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966). Of the exemplary rationales that may support a conclusion of obviousness, the Office here relies upon “some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to . . . combine prior art reference[s] teachings to arrive at the claimed invention.” *Id.* However, the Office’s asserted “teaching, suggestion, or motivation” is based merely on the elements of the pending claims being known in the art. Applicants respectfully submit that that reasoning is not enough.

It is known that “[a] prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention.” M.P.E.P § 2141.02(VI). Here, the Office’s assertions disregard relevant teachings of the cited references, thereby distorting what would be “fairly suggested” to one of ordinary skill in the art when viewing the references “as a whole.” See *In re Burckel*, 592 F.2d 1175, 1179, 201 U.S.P.Q. 67, 70 (C.C.P.A. 1970) (“[A] reference must be considered not only for what it expressly teaches, but also what it fairly suggests.”).

When viewed in its entirety, Follath, alone or in combination, fails to provide one of ordinary skill in the art any guidance to make the claimed invention. As acknowledged by the Office, Follath teaches treating patients suffering from heart failure with levosimendan, but does not teach treating patients suffering from severe renal failure. Indeed, patients suffering from “severe renal failure” were specifically excluded from the study. Follath at page 197, left column, ¶ 2. While the Office relies on secondary references to remedy this deficiency, Applicants respectfully submit that only in view of the pending claims would one of ordinary skill have been guided to link levosimendan treatment for patients suffering from severe renal failure.

Moreover, Follath indicates that “[s]erum creatinine concentration . . . declined in the levosimendan group,” but that the modest increase in renal and hepatic function was “possibly” due to “organ perfusion.” Follath at page 200, left column, ¶ 3. As discussed in the previous Response submitted November 18, 2009, while many vasoactive agents produce renal vasodilation and increase the renal blood flow in subjects with healthy renal function, such agents have failed to show benefits in subjects actually suffering from renal failure. Thus, one of ordinary skill in the art at the time of the invention understood that the renal vasodilatory effect of a vasoactive agent in healthy subjects does not guarantee success in the treatment of patients suffering from renal failure. Indeed, at the priority date of the present invention, no effective drug therapy existed for the treatment of renal failure, which is known to cause high mortality among patients. See, e.g., Bonventre et al., 1st paragraph, cited by the Office in the Office Action dated January 15, 2009 at page 3.

Further, a lack of beneficial renal effects from treatment with levosimendan in animals with renal failure was actually reported in Oldner et al. (cited in the previous Response submitted November 18, 2009). Therefore, the state of the art at the time of the invention would have been led away from treating patients suffering from severe renal failure with levosimendan.

Perrone and Pagel do not remedy the deficiencies of Follath, as Perrone is merely directed to a review of measuring serum creatinine levels as one indicator of renal function, and Pagel is only relied upon for the teaching of daily administration.

Thus, the art simply does not support an obviousness rejection, and Applicants respectfully request that the rejection be withdrawn.

III. Conclusion

In view of the foregoing remarks, Applicants respectfully request reconsideration of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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